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REMARKS

Claims 1-3, 5-16, 18-25, 27-34, 36-49 and 53-55 have been examined in this action. Applicants have herein above canceled claims 1, 3-4, 6, 12, 16-17, 19, 23, 25-27, 32, 34-36, 44-69 without prejudice to applicants' right to pursue the subject matter of these claims in a future continuation application. New claims 70-73 have been added, wherein these claims correspond to original dependent claims 3, 16, 25 and 34, which have been rewritten into independent form and original Claims 2, 5, 7, 8, 10, and 11 have been amended to depend on new claim 70 and claims 5 and 7 have also been amended to recite 'cardiac muscle' for which antecedent basis is found in new claim 70; original Claims 13, 14, 15, 18, and 21 have been amended to depend on new claim 71 and claims 15, 18 and 20 have also been amended to recite 'cardiac muscle' for which antecedent basis is found in new claim 71; original Claims 24, 28, 29, and 30 have been amended to depend on new claim 72 and claim 24 has also been amended to recite 'cardiac muscle' for which antecedent basis is found in new claim 72; and original claims 33 and 37 have been amended to depend on new claim 73 and claim 33 has also been amended to recite 'cardiac muscle' for which antecedent basis is found in new claim 73. No new matter is presented by this Amendment. Reconsideration and allowance of this application is respectfully requested.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-3, 5-16, 18-25, 27-34, 36-49 and 53-55

The rejection of Claims 1-3, 5-16, 18-25, 27-34, 36-49 and 53-55 has been maintained under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Without conceding the correctness of the Examiner's position, applicants have canceled claims 44-55 without prejudice to applicants' right to pursue the subject matter of these claims in a future continuation.

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Claims 1, 12, 23, 32, 39, 44 and claims dependent thereon

The Examiner has maintained the rejection of Claims 1, 12, 23, 32, 39, 44 and claims dependent thereon have been rejected under 35 U.S.C. § 112, second paragraph as being indefinite and unclear for the recitation of the term "effective".

The Examiner asserts that any amount that is added to some extent could be considered an effective amount and there is no limitation as to how much could be added to result in the desired effect.

Applicants respectfully traverse the Examiner's rejection and maintain that the term "effective" is definite and clear to one of skill in the art. The subject specification specifically teaches one of skill in the art what constitutes an effective amount of autologous BM-MNCs and provides a range of minimum and maximum amounts of cells to be administered per injection site. (See, Specification, *inter alia* at page 10, lines 1-3) Accordingly, it is clear that not just ***any*** amount produces the desired effect. Thus, one of skill in the art would understand the scope of the claims when read in light of the specification, i.e. the claims reasonably apprise one of skill in the art of the scope of the invention. Accordingly, the requirements of 35 U.S.C. § 112, second paragraph have been met. Therefore, applicants maintain that presently pending Claims 70-73 and claims dependent thereon are definite and distinctly claim the subject matter of the claimed methods.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 112, first paragraph

The rejection of Claims 1-3, 5-16, 18-25, 27-34, 36-49 and 53-55 under 35 U.S.C. § 112, first paragraph have been maintained as lacking an enabling disclosure for reasons of record.

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The Examiner asserts that although the isolation of EPCs from BM-MNCs may not be critical for the invention to work, other factors have not been taught to guide one of skill in the art to practice the full scope of the invention. The Examiner further asserts that growth factors such as cytokines have not been addressed in the specification and specific tissue locations which would be high in local growth factor concentrations. The Examiner cites Hamano et al. as stating that induction of angiogenesis is dependent on the presence of growth factors. The Examiner states that no specific limitations in the claims would lead one of skill to administer BM-MNCs to tissue ares that would induce growth factor secretion. The Examiner also asserts that the effects of BM-MNC administration to areas that are not conducive to differentiation has not been taught by the specification. For these reasons, the Examiner concludes that one of skill would be forced into large quantities of experimentation to practice the invention.

35 U.S.C. §112, first paragraph requires that an application provide an enabling disclosure:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same ...." (Emphasis added)

> The issue of enablement under 35 U.S.C. §112, first paragraph,
>
> ... requires determination of whether a person skilled in the pertinent art, using the knowledge available to such a person and the disclosure tin the patent document, could make and use the invention without undue experimentation. It is not fatal if some experimentation is needed, for the patent document is not intended to be a production specification. *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 941 (Fed. Cir. 1990) (Emphasis added)

In re Wands provides eight factors which serve as a guide to ascertain what constitutes undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed.Cir. 1988). These factors are 1) the quantity of experimentation necessary; 2) the amount of direction and guidance presented; 3) the presence or absence or working examples; 4) the nature of the invention; 5) the state of the prior

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art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims.

When applying the Wands' factors to the present invention, in particular the detailed direction and guidance in the specification for one of skill in the art, knowledge of the state of the art at the time of filing the instant application, and working examples, it is clear that the specification is fully enabling without undue experimentation for one of skill to make and use the claimed invention.

Accordingly, applicant respectfully traverses the Examiner's rejection and maintains that the specification as filed enables one of skill in the art to practice the full scope of claimed invention.

The Examiner's assertions about growth factors such as cytokines, tissue locations which would be high in local growth factor concentrations or areas that would induce growth factor secretion and effects of BM-MNC administration to areas not conducive to differentiation are all irrelevant to the claimed invention. The claims do not recite any of the above-mentioned factors and *need not recite them*, as they are *not* required for the practice of the claimed method. All that the claimed methods require is isolation of autologous bone marrow-mononuclear cells from the subject and transplantion locally into the cardiac muscle tissue of an effective amount of the autologous bone-marrow mononuclear cells, resulting in formation of new blood vessels in the cardiac muscle tissue.

One of skill in the art, guided by the teachings of the specification, is adequately enabled if the recited steps are performed and the recited therapeutic effects are obtained. In addition to the detailed amount of direction and guidance present in the subject specification, working examples are provided. The working examples demonstrate neovascular formation from BM-MNCs, thus confirming that the administration of the isolated BM-MNCs –without more-- adequately produces the desired effects as described and claimed, and thereby show one of skill

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in the art how to make and use the invention commensurate in scope with the claims without undue experimentation. Therefore, the enablement requirement is satisfied by the subject specification. Accordingly, presently pending Claims 70-73 and dependent Claims 2, 5, 7-11, 13-15, 18, 20-22, 24, 28-31, 33, 37-43 are fully enabled by the specification as filed.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §112, first paragraph.

Rejections under 35 U.S.C. § 102(b)

Kobayashi et al.

The rejection of Claims 1-8, 10, 12-13, 15-16, 18-21, 23-28, 30, 32-34, 36-37, 39-40, 42, 44-45, 47-49 and 53-54 under 35 U.S.C. § 102(a) as being anticipated by Kobayashi et al. (J. Surgical Res. 2000 Apr; 89(2):189-95) has been maintained.

Applicants respectfully traverse the Examiner's rejection and maintain that Kobayashi et al. does not disclose each and every element of the claimed methods of forming new blood vessels in tissue in a subject.

New independent claims 70-73, recite the method steps of: a) isolating autologous bone marrow-mononuclear cells from the subject; and b) transplanting locally into the cardiac muscle tissue an effective amount of the autologous bone-marrow mononuclear cells, resulting in formation of new blood vessels in the cardiac muscle tissue. All presently pending dependent claims recite these steps by virtue of their dependency on these independent claims.

Kobayashi et al. do not *isolate* the mononuclear cells from the bone marrow, as required by the claimed method. Rather, Kobayashi et al. collect bone marrow from rat femur and tibia and prepare bone marrow suspensions by pressing bone marrow segments through a fine wire mesh; red blood cells are removed by adding Tris-buffered ammonium chloride and the bone

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marrow cells are suspended in PBS. (See, Kobayashi et al. p. 190, Preparation of rat bone marrow cells) The bone marrow cells are labeled with intracellular fluorescent dye prior to implantation into ischemic heart.

The Examiner asserts that Kobayashi et al.'s isolation of autologous bone marrow cells anticipate the claimed isolation of mononuclear cells from bone marrow.

That is clearly not the case. Kobayashi et al.'s bone marrow cells only have red blood cell removed therefrom. Therefore, Kobayashi et al.'s injected population of bone marrow cells is not the same population of BM-MNCs, which are isolated as described in the subject specification *inter alia* at page 8, line 24 through page 9, line 9, and claimed in the pending claims. Since Kobayashi et al. do not teach each and every element of the claimed methods, Kobayashi et al. do not anticipate presently pending Claims 70-73 and dependent Claims 2, 5, 7-11, 13-15, 18, 20-22, 24, 28-31, 33, 37-43.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 102(a).

Shintani et al.

Claims 1-2, 5-8, 10-15, 18-21, 23-24, 27-30, 32-33, 36-37, 44-48, and 53-54 have been rejected under 35 U.S.C. § 102(a), as being anticipated by Shintani et al. (Circulation 1999 Nov 2; 100(18):I.406, Abstract).

Applicants have cancelled without prejudice independent claims 1, 12, 23, and 32 and generic dependent claims 6, 19, 27, and 36. New independent claims 70-73 all recite *cardiac muscle tissue* and claims dependent thereon also only recite such tissue by virtue of their dependency thereon.

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Shintani et al., describe intramuscular transplantation of bone-marrow derived mononuclear cells into *skeletal muscle*. Accordingly, Shintani et al. do not teach all of the elements of the claimed methods, i.e. transplantation of BM-MNCs into cardiac muscle tissue. Therefore, Shintani et al. do not anticipate presently pending new Claims 70-73 and dependent Claims 2, 5, 7-11, 13-15, 18, 20-22, 24, 28-31, 33, 37-43.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 102(a).

In view of the foregoing amendments and remarks, it is firmly believed that the subject invention is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

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